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Inhibition of multidrug resistance protein I (MRP1) improves chemotherapy drug response in primary and recurrent glioblastoma multiforme

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Glioblastoma multiforme (GBM) is a highly aggressive brain cancer with an extremely poor prognostic outcome despite intensive treatment. All chemotherapeutic agents currently used have no greater than 30-40% response rate, many fall into the range of 10-20%, with delivery across the blood brain barrier (BBB) or chemoresistance contributing to the extremely poor outcomes despite treatment. Increased expression of the multidrug resistance protein 1(MRP1) in high grade glioma, and it's role in BBB active transport, highlights this member of the ABC transporter family as a target for improving drug responses in GBM. In this study we show that small molecule inhibitors, and gene silencing, of MRP1 had a significant effect on GBM cell response to Temozolomide (150μM), Vincristine (100nM) and Etoposide (2μM). Pre-treatment with Reversan (inhibitor of MRP1 and P-glycoprotein) led to a significantly improved response to cell death in the presence of all three chemotherapeutics, in both primary and recurrent GBM cells. The presence of MK571 (inhibitor of MRP1 and Multidrug resistance protein 4(MRP4) led to an enhanced effect of Vincristine and Etoposide in reducing cell viability over a 72 hour period. Specific MRP1 inhibition led to a significant increase in Vincristine and Etoposide-induced cell death in all three cell lines assessed. Treatment with MK571, or specific MRP1 knockdown, did not have any effect on Temozolomide drug response in these cells. These findings have significant implications in providing researchers an opportunity to improve currently used chemotherapeutics for the initial treatment of primary GBM, and improved treatment for recurrent GBM patients. This work is funded by Irish Cancer Society Research Fellowship CRF13TIV, supported by Tesco Charity of the Year.

Biography

Tivnan has completed her primary degree in Science – Biochemistry and continued to complete her PhD in Genetics from Trinity College Dublin, Ireland. Amanda is a unique, independent and highly motivated researcher, a mother of two, who has progressed her academic career at exceptional pace and with exemplary rigor and strength. Her studies have made use of an elegant blend of cancer research, neurooncology and neuroscience, as well as molecular biology and drug delivery research to yield novel data with substantial clinical and therapeutic significance.

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